IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOVAIL LABORATORIES INTERNATIONAL SRL a corporation of Barbados,	)	
Plaintiff,	)	C.A. Nos. 05-586 (GMS) 05-730 (GMS)
v.	)	06-620 (GMS)
	)	(CONSOLIDATED)
ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION,	)	
Defendants.	)	

BIOVAIL'S OPENING CLAIM CONSTRUCTION BRIEF

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NATURE AND STAGE OF THE PROCEEDING

Plaintiff Biovail Laboratories International SRL ("Biovail") filed this patent infringement suit under the Hatch-Waxman Act against Andrx Pharmaceuticals, LLC and Andrx Corporation ("Andrx"), after Andrx filed an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA") seeking approval to market generic versions of Biovail's highly successful blood pressure medication Cardizem® LA. In consolidated suits, Biovail sued Andrx for infringement of U.S. Patent Nos. 5,529,791 (the "'791 patent") and 7,108,866 (the "'866 patent").

Biovail submits this brief in support of its constructions of the disputed terms of the '791 and '866 patents. The parties' final joint claim construction charts have been docketed as D.I. 142.

SUMMARY OF ARGUMENT

Biovail's constructions are firmly grounded in the plain language of the claims and are consistent with the patent specifications, file histories, and understanding of those skilled in the art. In stark contrast, Andrx's constructions ignore the plain language of the claims and are unmistakably strained constructions fueled by Andrx's non-infringement arguments.

The first patent at issue, the '791 patent, concerns novel once daily formulations of the drug diltiazem, which in the human body, maintain diltiazem in a soluble (dissolved or liquid) state to afford continued gradual release of the drug. The '791 patent teaches that solubility is maintained through an "admixture" of diltiazem salts and a wetting agent. The wetting agent is selected from the group of wetting agents identified in Claim 1, including sugars. Under Biovail's constructions, the required admixture can be found at a point in time during the life of the compositions, in particular

during *in vivo* (*i.e.*, in the body) transit from the stomach to the less acidic environment of the intestinal tract. This is consistent with the plain language of Claim 1 which states that the purpose of the admixture is "to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is ***unaffected by the pH of the gastrointestinal tract*** . . . ." Thus, according to the plain words of the claim, the only way to determine if the admixture is performing as required is to evaluate the performance of the composition as it passes -- through the body -- into the "***pH of the gastrointestinal tract***." Biovail's *in vivo* construction of the '791 patent claims is thus compelled by the plain words of the claims themselves.

Andrx's constructions, on the other hand, are motivated by an obvious attempt to avoid Biovail's expert proofs establishing that Andrx's proposed products form the required *in vivo* admixture of diltiazem salts and wetting agent. Biovail has expert testing demonstrating that Andrx's tablet products contain the claimed "admixture" in *in vivo* conditions. Andrx has no testing, or other answer, to rebut these proofs. Andrx therefore necessarily needs to limit the '791 patent claims to pharmaceutical compositions in a dry, pre-ingested state. In so doing, Andrx asks the Court to ignore the plain language of the '791 patent claims, and consequently the purpose of the invention. As explained in further detail below, Andrx's constructions add limitations to unambiguous claim language, and in other cases, simply rewrite claim language to fit its claim constructions.

The second patent at issue, the '866 patent, concerns novel once daily formulations of diltiazem that are suitable as chronotherapeutic medications. Chronotherapeutics are pharmaceutical compositions that deliver the correct amount of

medication to the correct site of action at the most appropriate time period for a particular disease or condition. The greatest incidence of adverse cardiovascular events such as stroke and heart attack occurs during the early morning waking hours when blood pressure is rising in response to the natural circadian rhythm of the body. The formulations of the '866 patent provide the maximum levels of drug during these critical waking hours. The '866 patent claims recite certain *in vitro* (in a controlled experimental environment, such as a laboratory vessel, rather than in the body) and *in vivo* characteristics of those formulations. Biovail's constructions, as is the case with the '791 patent, rest on the plain language of the claims and are entirely consistent with the intrinsic record.

Andrx's constructions, on the other hand, improperly read language from the patent specification and extrinsic evidence into the claims. Further, as explained in more detail below, Andrx oversteps the bounds of sound claim construction principles in asking the Court to make factual determinations as to the meaning and interpretation of extrinsic evidence.

STATEMENT OF FACTS

A. THE '791 PATENT

The '791 patent is directed to novel extended-release formulations of the drug diltiazem. [1 A-4 (2:9-15).][1] Diltiazem is used, either alone or in combination with other medicines, in the treatment of hypertension and angina pectoris. [1 A-4 (1:18-20).]

[1] Citations to the Joint Appendix of Intrinsic and Extrinsic Evidence are in the following format: "[Tab#] A-[page#]." Thus, a citation to "2 A-10" would refer to tab 2, page A-10. Patent citations are by column and line number, in the following format: "[Tab#] A-[page#] (column:line).]" The parties will file the Joint Appendix with their Answering Briefs on April 24, 2007.

Diltiazem is a base that can be solubilized (dissolved or made liquid) when it is made into an acid addition salt, such as the hydrochloride salt. [Brenner ¶ 25.][2] When the pH of solutions of the hydrochloride salt increases (*i.e.*, the solutions become less acidic), the concentration of the less soluble form of the drug -- the free base -- in the solution increases. [Brenner ¶ 25.] When the concentration of the less soluble, free base, form of the drug increases in a less acidic solution environment, the drug will precipitate from solution, *i.e.*, form solid particles. [Brenner ¶ 25.] These solid particles are useless to provide the desired antihypertensive effect of diltiazem in the body. [Brenner ¶ 25.] Therefore, as the dissolved diltiazem hydrochloride salt goes from an acidic environment to a less acidic environment, for example, from the acidic environment of the stomach to the less acidic environment of the intestine, it becomes less soluble and solid particles of diltiazem can precipitate. [Brenner ¶ 25.] Such precipitation is undesirable because it results in a loss of the amount of therapeutically effective diltiazem available to the body. [Brenner ¶ 25.] An important consideration, therefore, in formulating an extended-release form of diltiazem hydrochloride is to make sure that the formulation avoids the potential for the diltiazem to precipitate out -- ***from solution*** -- during the *in vivo* transit of the drug through the gastrointestinal tract. [Brenner ¶ 26.]

The formulations claimed in the '791 patent provide for a delivery system that, among other things, ensures that the solubility of the dissolved diltiazem is maintained as the formulation moves from the stomach through the intestines. [Brenner

[2] "Brenner ¶ __" refers to the accompanying Declaration of Gerald S. Brenner, Ph.D., which is submitted to explain the background of the technology at issue as expressly permitted. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1318 (Fed. Cir. 2005).

¶ 27.] The '791 formulations employ the use of a plurality of membrane-based beads containing the active drug, diltiazem hydrochloride, that may be filled into gelatin capsules or compressed into tablets. [Brenner ¶ 27.]

The absorption of drugs into the body from membrane-based dosage forms comprises several stages. [Brenner ¶ 10.] The first stage requires solubilization of the drug beneath the membrane. [Brenner ¶ 11.] The second stage requires transport of the solubilized drug across the membrane. [Brenner ¶ 12.] The third stage involves absorption of the drug from the gastrointestinal tract, and into the body. [Brenner ¶ 13.] Problems can develop in the absorption process described above if the drug dissolves too slowly, or if the drug once dissolved comes out of solution. [Brenner ¶ 14.]

A key teaching of the '791 patent is that the solubility of dissolved diltiazem is maintained through a homogeneous admixture of diltiazem and a wetting agent (Brenner ¶ 28):

> . . . one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ***ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet*** . . . .
> [1 A-7-8 (8:63-9:2) (emphasis added).]

The '791 patent teaches, for example, that sugar is one such wetting agent. [Brenner ¶ 28.] As the '791 inventors explained to the Patent Office during prosecution, "[t]his particular combination is important as it ensures that the solubility of the active ingredient Diltiazem is unaffected by the ***pH of the gastrointestinal tract***," *i.e.*, diltiazem does not precipitate out -- ***from solution*** -- during *in vivo* transit through the gastrointestinal tract. [Brenner ¶ 29.]

Biovail asserts that Andrx infringes Claims 1 and 2 of the '791 patent. Claim 1 of the '791 patent, which is the only independent claim of the patent, reads, in pertinent part, as follows:

> An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid-, and base- insoluble polymer and a pharmaceutically-acceptable adjuvant, and wherein the wetting agent is selected from the group consisting of sugars . . . . [1 A-7-8 (8:59-9:8).]

B. THE '866 PATENT

The '866 patent is directed to once daily formulations of diltiazem, suitable for evening administration to patients suffering from hypertension and/or angina pectoris. [12 A-126 (1:13-17).] The formulations of the '866 patent are described as chronotherapeutic formulations. [12 A-127 (4:62-67).] Chronotherapeutics relies on the practice of delivering the correct amount of drug to the correct site of action at the most appropriate time period for the particular disease or condition. [12 A-126 (1:39-42).] The '866 patent teaches that human blood pressure does not remain constant during day and night. [12 A-126 (1:42-43).] Early in the morning blood pressure begins to rise from the low levels reached during sleep. [12 A-126 (1:43-44).] Such increases in blood pressure are accompanied by increases in heart rate, and studies have indicated that the greatest incidence of heart problems such as stroke, heart attack, myocardial ischemia

(pathological loss or reduction in blood flow to the heart) and sudden cardiac death occur during the early morning waking hours when the blood pressure is rising in response to the natural circadian rhythm. [12 A-126 (1:45-52).] After normally rising in the morning, blood pressure remains elevated during the day until, generally, early evening when it starts to fall to its lowest level during sleep. [12 A-126 (1:52-55).]

The formulations of the '866 patent provide diltiazem preparations suitable for once-a-day administration in the evening for providing effective amounts of diltiazem in the morning, when blood pressure begins to rise from the low levels reached during sleep. [12 A-127 (4:62-67).]

Biovail asserts that Andrx infringes Claims 1, 2, 4, 5, 6, 39-44, 65, 81, 86 and 88 of the '866 patent. Claim 1 of the '866 patent, which is the only independent claim of the patent, reads, in pertinent part, as follows:

> An orally administrable controlled-release composition comprising a pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof . . . said orally administrable composition:
> A) in vitro exhibits the following in vitro release characteristics;
> (i) releases the diltiazem or a pharmaceutically acceptable salt thereof into an aqueous medium at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
> (a) between about 1% and about 15% after about 2 hours;
> (b) between about 7% and about 35% after about 4 hours;
> (c) between about 30% and about 58% after about 8 hours;
> (d) between about 55% and about 80% after about 14 hours;
> (e) in excess of about 75% after about 24 hours; and/or
> (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

> (a) between about 1% and about 25% after about 2 hours;
> (b) between about 7% and about 45% after about 4 hours;
> (c) between about 30% and about 68% after about 8 hours;
> (d) in excess of about 75% after about 24 hours; and further wherein said orally administrable composition having said in vitro release characteristics results in a composition that:
> B) when orally given to humans exhibit the following properties:
> (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
> (ii) bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria; and
> (iii) provides a Cmax of diltiazem in the blood at between about 10 hours and 15 hours after administration. [12 A-137 (23:19-24:22).]

C. THE FEDERAL CIRCUIT'S PRIOR CONSTRUCTION OF THE '791 PATENT CLAIM TERM "ADMIXTURE"

The construction of the '791 patent claim term "admixture" was the subject of a prior litigation between Biovail and Andrx concerning different Andrx products. In that litigation, the district court believed that the '791 patent claims required a showing of the "admixture" in the dry state. *Biovail Corp. v. Andrx Pharms., Inc.*, 158 F.Supp. 2d 1318, 1329 (S.D. Fla. 2000). On appeal, the Federal Circuit did not adopt the district court's construction, and expressly left open the possibility of an *in vivo* claim construction. *Biovail Corp. v. Andrx Pharms., Inc.*, 239 F.3d 1297, 1301 (Fed. Cir. 2001).[3] Further, the Federal Circuit held that the "admixture" of diltiazem salt and

[3] The Federal Circuit also did not adopt the district court's construction that despite the plain language of Claim 1 of the '791 patent, "sugars" are not wetting agents. *Biovail Corp.*, 239 F.3d at 1303. This aspect of the district court's claim construction was clearly flawed. Indeed, even Andrx now concedes that the term "wetting agent" specifically includes "sugars." [D.I. 142.]

wetting agent of the '791 patent claims must be "homogeneous." *Id.* at 1302. The court did not define "homogeneous."

ARGUMENT

A. CLAIM CONSTRUCTION STANDARDS

"It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)). Claims "are generally given their ordinary and customary meaning." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The Federal Circuit has made plain that "the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1313.

To determine the "ordinary and customary" meaning of a claim term, courts first examine the intrinsic evidence which consists of the language of the claims, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1315 (quoting *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998) ("The best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history.")). Indeed, "[t]he claims, specification, and file history, rather than extrinsic evidence, constitute the public record of the patentee's claim, a record on which the public is entitled to rely." *Vitronics*, 90 F.3d at 1583. If claim construction is not founded on this public record, the public notice

function of patents will be undermined. *Phillips*, 415 F.3d at 1319 (citing *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1578 (Fed. Cir. 1995)).

In construing the claims based on the specification, *Phillips* also cautioned that courts must "avoid the danger of reading limitations from the specification into the claims." *Phillips*, 415 F.3d at 1323. "The written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of the claims." *Phillips*, 415 F.3d at 1312 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995). *See Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1211 (Fed. Cir. 2007) (holding that the district court erred in limiting the term "pharmaceutically acceptable polymer" to hydrophilic, water-soluble compounds selected from a list given in the written description). The *Phillips* court also acknowledged "the distinction between using the specification to interpret the meaning of a claim and importing limitations from the specification into the claim can be a difficult one to apply in practice." *Phillips*, 415 F.3d at 1323. That court further warned against restricting the claims only to specific embodiments of the invention described in the specification and noted that the Federal Circuit has "expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment." *Phillips*, 415 F.3d at 1323 (citing *Gemstar-TV Guide Int'l, Inc. v. Int'l Trade Comm'n*, 383 F.3d 1352, 1366 (Fed. Cir. 2004).

When reviewing the prosecution history to further clarify the specification, the Federal Circuit has distinguished between using the prosecution history in defining a claim term and the doctrine of prosecution history estoppel used to impose a limitation on the range of equivalents if literal infringement is not found after properly construing the

claims. *See Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001) ("a claim term should be construed consistently with its appearance in other places in the same claim or in other claims of the same patent.")

While courts can always rely on experts to explain the background technology at issue, explain how the invention works, or to ensure that the court's understanding of technical aspects of the patent is consistent with that of a person of ordinary skill in the art (*Phillips*, 415 F.3d at 1318), "[i]n most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence." *Vitronics*, 90 F.3d at 1583. However, if after examining all the intrinsic evidence, further clarification of a claim term is required, the Federal Circuit has "authorized district courts to rely on extrinsic evidence, which 'consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises.'" *Phillips*, 415 F.3d at 1317 (quoting *Markman*, 52 F.3d at 980). However, the Federal Circuit has noted that extrinsic evidence is generally less reliable than the patent itself and the prosecution history in construing claim terms because it is not part of the patent and was not created at the time of the patent prosecution to explain the patent's scope and meaning. *Phillips*, 415 F.3d at 1318. The *Phillips* court also recognizes another serious issue with extrinsic evidence:

> [T]here is a virtually unbounded universe of potential extrinsic evidence of some marginal relevance that could be brought to bear on any claim construction question. In the course of litigation each party will naturally choose the pieces of extrinsic evidence most favorable to its cause, leaving the court with the considerable task of filtering the useful extrinsic evidence from the fluff.
> *Phillips*, 415 F.3d at 1318.

B. CLAIM CONSTRUCTION OF THE '791 PATENT

Biovail's constructions originate from the plain language of the claims and are consistent with the patent specification, the patent file history, and the understanding of those skilled in the art.

Claim 1 of the '791 patent reads, in pertinent part, as follows:

> An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid-, and base- insoluble polymer and a pharmaceutically-acceptable adjuvant, and wherein the wetting agent is selected from the group consisting of sugars . . . .[1 A-7-8 (8:59-9:8).]

1. "admixture"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"admixture"	means a homogeneous admixture of one or more diltiazem salts and wetting agent can be found at a point in time during the life of the compositions, in particular during their *in vivo* transit from the stomach to the less acidic environment of the intestinal tract. Thus, a formulation will satisfy the admixture language of the '791 patent claims if the formulation is exposed to pH conditions that are found in the gastrointestinal tract, and operates such that beads of the formulation include a homogeneous admixture of one or more diltiazem salts and wetting agent in those conditions. The term homogenous means having one or more salts of diltiazem and wetting agent throughout the admixture of one or more salts of diltiazem and wetting agent.	Admixture means two or more items that are commingled and interdispersed to obtain a homogeneous product (in this case, bead). In addition, the claim language "each bead containing . . . wetting agent in admixture with the one or more diltiazem salts" requires that the entirety of the bead be homogeneous. The term "homogeneous" means that samples taken anywhere within the bead have identical compositions. Admixture should be read to refer to the dried, uncoated bead that is subsequently coated with a microporous membrane and included in the galenical composition.

Biovail addresses the disputed term "admixture" first, as this term is central to the '791 invention and sets the tone for understanding the entirety of the '791 patent claims.

The plain words of Claim 1 state that the purpose of the admixture is "***to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract . . . .***" [1 A-5 (3:65-68) (emphasis added).] Thus, according to the plain words of the claim, the admixture finds its purpose *in vivo* (in the gastrointestinal tract) and is therefore required *in vivo* to maintain the solubility of diltiazem. Indeed, the concept of a wetting agent in the dry state is nonsensical. Only when the drug is dissolved in the liquid state -- an event that

occurs in the body -- is it possible to determine whether the wetting agent satisfies the function required by the claims.

The '791 patent specification teaches that the *in vivo* performance of the claimed formulations is critical and is what makes them unique. For example, the specification states that the invention provides formulations of diltiazem having excellent biovailability (the extent to which a drug is available for use by the body). [1 A-4 (2:13-15).] Indeed, the only two figures in the '791 patent are plots of the concentration of diltiazem in the blood versus time, demonstrating the unique smooth *in vivo* drug release performance of these formulations. [Brenner ¶ 22.] Further, the '791 patent specification states that formulations of the invention gradually release diltiazem into the blood stream in a relatively uniform manner. [1 A-4 (2:27-32).] The specification also states that "it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range" and that formulations of the invention have "extended-release in the gastro-intestinal tract." [1 A-4 (2:48-53); 1 A-5 (4:20-24).] Paramount to the *in vivo* performance of the claimed formulations is the required admixture of diltiazem and wetting agent. Without the admixture, solid diltiazem particles could form resulting in lower bioavailability (less amounts of the drug to the patient) and disruption of the gradual release of the drug into the blood stream. [Brenner ¶ 30.] In other words, only if the wetting agent performs its required function *in vivo* can the disclosed benefits of the claimed formulations be realized. [Brenner ¶ 30.]

The '791 patent file history further compels an *in vivo* construction of the term "admixture" as well as the '791 patent claims as a whole. Specifically, in the June 22, 1992 submission to the Patent Office, the inventors distinguished the *in vivo*

performance of their formulations from that of U.S. Patent No. 4,960,596 ("Debregeas"). Debregeas discloses: (1) formulations with diltiazem applied to a sugar (saccharose) core surrounded by a membrane consisting primarily of shellac (70 parts) and ethylcellulose (30 parts), and (2) formulations with diltiazem applied to a sugar core surrounded by a membrane consisting primarily of ethylcellulose and dibutylsebacate. [Brenner ¶ 33.] The inventors explained to the Patent Office that the sugar in the core of Debregeas cannot act as a wetting agent because the Debregeas formulations do not provide an opportunity for the sugar to form a homogeneous admixture with diltiazem hydrochloride:

> … Debregeas does not disclose saccharose as a wetting agent. The saccharose contained in the central core of the bead cannot act as a wetting agent because in order to do so the saccharose must be mixed with the Diltiazem, and therefore, must be in solution with Diltiazem. ***Unfortunately, in this system saccharose can only end up in solution after all the layers of Diltiazem are dissolved***. In other words, saccharose can only become effective when there is not longer a need therefore. [2 A-21 (June 22, 1992 Amendment, p. 13) (emphasis added).]

As indicated above, the sequence of events of the Debregeas formulations *in vivo* is that first the membrane would be disrupted, followed by exposure of the drug layer to the aqueous environment. [Brenner ¶ 35.] Finally, after the drug layer is dissolved and enters the gastrointestinal tract, the sugar core is then exposed to the aqueous environment and dissolves. [Brenner ¶ 35.] Thus, the wetting agent (*i.e.*, sugar) never has the opportunity to form an admixture in the bead (*i.e.*, within the non-ruptured membrane) prior to the drug entering the gastrointestinal tract and being exposed to its less acidic environment. [Brenner ¶ 35.]

This sequence of events corresponds to the understanding of one of ordinary skill in the art. For example, the membrane of the Debregeas shellac/ethylcellulose formulations consists primarily of shellac (70 parts), and ethylcellulose (30 parts). [Brenner ¶ 36.] Shellac is an enteric coating material that will become soluble in the intestine. [Brenner ¶ 36.] Therefore, as shellac solubilizes, the membrane will be disrupted, thus allowing drug to leave before it has an opportunity to homogeneously mix with sugar. [Brenner ¶ 36.]

Tellingly, if the inventors intended to the limit their invention to formulations in a dry, pre-ingested state, there would have been no need and no reason whatsoever for them to distinguish their invention based on the *in vivo* performance of Debregeas.

Moreover, the file history is replete with statements that make plain that *in vivo* performance is the key criteria for the "admixture," and the '791 invention as a whole. For example, the inventors explained that:

> The wetting agents claimed in the present invention are substances which are believed to modify the solubility of Diltiazem inside the coated beads when they are ***placed in a dissolution medium or when they are ingested by a mammal***. This concept is neither disclosed nor suggested by Debregeas et al. [2 A-21 (June 22, 1992 Amendment, p. 13) (emphasis added).]

* * *

> By contrast [to Debregeas], the present formulation contains Diltiazem or one or more salts thereof in admixture together with the wetting agent. By combining the wetting agent in admixture with Diltiazem or one or more salts thereof, the solubility of the Diltiazem may be controlled and rendered independent of pH. This is quite important due to the wide variation ***in pH in the gastrointestinal tract***. [4 A-51-52 (April 26, 1993 Amendment, pp. 9-10) (emphasis added).]
>
> * * *
>
> In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by ***pH or other adverse conditions in the gastrointestinal tract***. . . This control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours. [5 A-71 (May 28, 1993 Amendment, p. 8) (emphasis added).]
>
> * * *
>
> This particular combination is important as it ensures that the solubility of the active ingredient Diltiazem is unaffected by the ***pH of the gastrointestinal tract***. This affords excellent bioavailability while avoiding plasmatic concentration peaks. [6 A-88 (December 14, 1995 Amendment, p. 5) (emphasis added).]

Andrx's constructions mainly originate from Andrx's non-infringement arguments. Biovail's expert proofs demonstrate that Andrx's proposed tablet products form the required *in vivo* admixture of diltiazem and wetting agent. Andrx seeks to avoid Biovail's proofs by taking a claim construction position inherently at odds with the plain language of the '791 patent claims and the invention. Andrx argues that the '791 patent claims should be limited to pharmaceutical compositions in a dry, pre-ingested state. Such a strained construction turns the claim language of the '791 patent on its head. Moreover, Andrx's argument finds no basis in law. The Federal Circuit has already

decided that a patent claim for a drug may extend to the drug after it has been ingested. *Zenith Labs, Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1421-22 (Fed. Cir. 1994).

Andrx's construction of the term "admixture" is that it should refer to a "dried, uncoated bead." This makes no sense. The plain language of Claim 1 uses the term "admixture" and the term "beads" in the same clause. This means that those terms are not synonymous. *See Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 93 F.3d 1572, 1579 (Fed.Cir.1996) (stating that if two terms described a single element, "one would expect the claim to consistently refer to this element [with one or the other of the two terms], but not both, especially within the same clause.") In addition, Claim 1 states that the "beads" contain the "admixture" so the plain language of the claim dictates that the terms are different. Further, as the plain language of Claim 1 states, the purpose of the admixture is "***to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract . . . ."*** [1 A-5 ('791 patent, 3:65-68) (emphasis added).] Thus, the "admixture" finds its purpose *in vivo* (in the gastrointestinal tract) because only in that environment is there a need to maintain the solubility of diltiazem. In the dry, pre-ingested state, solubility is not an issue.

As stated above, the Federal Circuit held that the term "admixture" means "homogeneous admixture," but did not define "homogeneous." *Biovail Corp. v. Andrx Pharms., Inc.*, 239 F.3d 1297, 1302 (Fed. Cir. 2001). The meaning of "homogeneous" is "uniform in structure or composition throughout". [7 A-95.] Thus, the "homogeneous admixture" of the '791 patent claims refers having one or more salts of diltiazem and the wetting agent throughout the required admixture.

Andrx, on the other hand, argues that "homogeneous" means that samples taken anywhere within the ***bead*** have ***identical*** composition. Andrx's construction is belied by the Federal Circuit which held that the ***admixture*** -- and not the bead -- must be homogeneous. *See Biovail Corp.*, 239 F.3d at 1302. Moreover, even the dictionary definition relied upon by Andrx does not state "homogeneous" means identical in composition. It states "1. composed of parts all of the same kind . . . 2. of the same kind or nature; essentially alike . . . ." [9 A-101.] As such, Andrx's construction contradicts the Federal Circuit's holding, and finds no support within the dictionary itself.

2. "extended-release galenical composition"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"extended-release galenical composition"	a pharmaceutical composition that releases the active ingredient over an extended period of time	This limitation means a pharmaceutical composition as it is prepared in the dry state and before ingestion by a patient, that releases the active ingredient over an extended period of time.

Biovail's construction is consistent with the term's plain meaning. First, one of ordinary skill in the art would understand the term galenical to be an umbrella term covering all types of pharmaceuticals, dry and liquid, such as liquid filled capsules, tablets, injectables and syrups. [Brenner ¶ 16.] Second, the plain language of the claim refers to the "pH of the gastrointestinal tract or other adverse conditions which the ***composition*** will meet." Thus, the claim itself specifies that the composition exists in the wet *in vivo* environment.

Andrx's construction not only ignores the purpose of the '791 invention, but it would mean that pharmaceutical compositions that are not dry, such as liquid filled capsules, injectables and syrups, are not even galenical or pharmaceutical compositions. Further, according to Andrx's construction, the composition would cease to exist once it

is ingested or exposed to pH conditions of the gastrointestinal tract. If that was the intended meaning or how one of ordinary skill in the art would understand it, then the claim language of the '791 patent would make little sense. *See Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001) ("a claim term should be construed consistently with its appearance in other places in the same claim or in other claims of the same patent.").

3. "beads"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"beads"	the structure wherein the wetting agent is in admixture with one or more diltiazem salts to maintain the solubility of the diltiazem when the composition is exposed to pH conditions of the gastrointestinal tract or other adverse conditions the composition will meet *in vivo*.	This limitation refers to the dry, uncoated material that is subsequently coated with a microporous membrane to form the galenical composition referred to in the claim.

The plain language of Claim 1 of the '791 patent states that "beads" are the structures wherein the wetting agent is in admixture with one or more diltiazem salts to maintain the solubility of the diltiazem when the composition is exposed to pH conditions of the gastrointestinal tract or other adverse conditions the composition will meet *in vivo*. [1 A-7 (8:62-9:2).] Specifically, Claim 1 states that there is "an effective amount of wetting in admixture with the one or more Diltiazem salts ***to maintain the solubility of the Diltiazem in each bead***, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet." [1 A-7 (8:62-9:2) (emphasis added).] This claim language unambiguously provides that there will be "beads" containing diltiazem salts and wetting agent in the soluble or dissolved state. This only occurs in an aqueous environment, *e.g.*,

in vivo. Indeed, as discussed above, the need to maintain diltiazem's solubility only arises when the formulation is in pH conditions of the gastrointestinal tract.

Without any support whatsoever, Andrx seeks to add a dry state limitation to the term "bead." Such a construction would render the Claim 1 meaningless Claim 1 expressly states that the purpose of the wetting agent is to "maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract."

4. "each bead"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"each bead"	refers to the beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient. This term does not require that every single bead of the composition contain diltiazem salt and wetting agent in admixture.	The "each bead" limitation requires that every single bead must contain diltiazem salt and wetting agent in admixture.

Biovail's construction of the term "each bead" is consistent with proper claim construction principles. Claim 1 uses the open ended phrase "comprises" when first referring to beads. According to the plain language of the claim the composition may comprise beads containing an effective amount of one or more said diltiazem salts as the active ingredient. Because of the use of the term "comprises" the formulation may also include other types of beads, *e.g.*, as cushioning beads to help preserve the integrity of the beads when compressing them into tablets. *See AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1245-46 (Fed. Cir. 2001) ("We have consistently held that the word 'comprising' is an open transition phrase" and that "its scope may cover devices that employ additional, unrecited elements."). Thus, when the claim refers to each bead,

it can only be referring to the particular beads mentioned, *i.e.*, beads containing an effective amount of one or more of said diltiazem salts as the active ingredient.

Andrx's construction requires that every bead within the formulation contain diltiazem salt and wetting agent in admixture. This construction ignores the plain language of the claim and violates established claim construction principles.

5. "an effective amount of wetting agent"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"an effective amount of wetting agent"	an amount of wetting agent sufficient to maintain the solubility of the diltiazem in each bead, ensuring that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.	An effective amount of wetting agent means an amount of wetting agent that acts within each bead to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein as further required by the claim language.

The plain language of the claim indicates that "an effective amount of wetting agent" is an amount of wetting agent "to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract . . . ." Nothing in the language of Claim 1 states or suggests that the wetting agent only serves its purpose within the beads. To the contrary, the plain language of the claim states that the wetting agent "ensures" that the solubility of the diltiazem is maintained as the composition moves though the gastrointestinal tract and releases the diltiazem into the body.

Andrx's construction adds a limitation to the claims that the wetting agent must "act within each bead" to maintain the solubility of the diltiazem. Andrx's construction is inconsistent with the plain language of the claim terms as "an effective

amount of wetting" says nothing about where the wetting agent acts. Andrx is plainly trying to rewrite the claim language.

6. "to maintain the solubility of the Diltiazem in each bead"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"to maintain the solubility of the Diltiazem in each bead"	means the wetting agent does not permit the solubility of the diltiazem to be affected by the pH or other adverse conditions of the gastrointestinal tract in a manner that would prevent a gradual release of the drug in a relatively uniform manner. The term solubility means the condition of being soluble. The term "each bead" refers to the beads containing an effective amount of one or more of said diltiazem salts as the active ingredient.	This limitation requires that the numerical value of the solubility of the free base diltiazem be maintained, i.e., be held constant in every single bead. "Solubility" refers to the amount of material (expressed in units of mass) that are capable of being dissolved in an amount of solvent to give a saturated solution (expressed in units of volume) at a given temperature.

Biovail's construction is consistent with the plain language of Claim 1 as well as the inventors' explanation to the Patent Office:

> In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by pH or other adverse conditions in the gastrointestinal tract. . . This control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours. [4 A-51 (April 26, 1993 Amendment).]

Thus, the purpose of the invention is to make certain that diltiazem remains soluble (liquid or dissolved) in the pH of the gastrointestinal tract so that diltiazem can be absorbed into the body. As the patent demonstrates, particularly in figures 1 and 2, the inventors knew their invention was working based on the extent of drug release into the body and the smooth plasma profile of the formulations. *See Applera Corp. v. Micromass UK Ltd.*, 186 F.Supp.2d 487, 523-24 (D. Del. 2002) (In construing "maintain such kinetic energies at a relatively low value," this Court rejected defendant's attempt to

imply that "maintain" meant "never vary" or "never fluctuate" and held that "maintain" was "used in [its] ordinary sense and [requires] no further construction." This Court stated that "[t]he claims do not require that the kinetic energy of ions never fluctuate. Indeed the kinetic energies of ions may fluctuate greatly, as long as the kinetic energy of those ions does not surpass the relatively low value or level required by the claim.") *Id.*

Andrx's construction focuses on the term "maintain," and asserts that the disputed claim terms means maintaining a certain numerical value for the solubility of diltiazem. Andrx's construction is contrary to the ordinary meaning of "maintain" and unsupported by the record. There is nothing in the patent specification or patent file history that suggests or even indicates that the inventors ever measured or even attempted to measure the solubility of diltiazem, and then further tried to "maintain" it at a specific numerical value.

7. "ensuring that the solubility of the Diltiazem is by unaffected the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"ensuring that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein"	means the wetting agent does not permit the solubility of the diltiazem to be affected by the pH or other adverse conditions of the gastrointestinal tract in a manner that would prevent a gradual release of the drug in a relatively uniform manner. The term solubility means the condition of being soluble.	This limitation requires that the wetting agent be homogeneously admixed with the diltiazem salt so that the wetting agent will act in the composition to ensure the solubility of diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions the composition would meet if and when the composition is ultimately ingested by a patient. These adverse conditions can include changes in ionic strength, changes in temperature, or changes in pH.

Biovail's construction relies on the plain language of the claims as well as the inventors' explanation to the Patent Office:

> In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by pH or other adverse conditions in the gastrointestinal tract . . . This control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours. [4 A-51 (April 26, 1993 Amendment).]

The claims unambiguously state that the composition "***will meet***" the pH of the gastrointestinal tract and other adverse conditions presented by the human body.[4] Thus, the claim clearly contemplates that the diltiazem has already been ingested when solubility becomes an issue. Andrx's construction is the result of its persistent denial that the '791 patent compel an *in vivo* claim construction. Andrx seeks to rewrite the claim terms to state that the wetting agent ensures the solubility of Diltiazem is unaffected by the pH of gastrointestinal tract or other adverse conditions the composition "***would meet*** if and when the composition is ultimately ingested by a patient." [emphasis added.] This is simply not the claim language.

8. "said beads being coated with a microporous membrane"

'791 Claim Terms	Biovail's Construction	Andrx's Construction
"said beads being coated with a microporous membrane"	means that the beads have a microporous membrane.	This limitation refers to the membrane that is to be placed on the outside of each bead which is capable of forming micropores that contains the ingredients referred to later in the claim.

The plain language of the claim states that the beads have a microporous membrane -- "said beads being coated with a microporous membrane." In other words,

[4] To the extent that Andrx seeks to read a list of purported "adverse conditions" into the claim this is improper and unsupported by the intrinsic record.

claim expressly requires two things: (1) that the beads are coated with a membrane, and (2) that the membrane is microporous.

Andrx's construction ignores the express claim language and suggests that the beads will be coated at some point in the future and that the membrane only be "capable" of forming micropores. In addition and, again, without any support whatsoever, Andrx seeks to add a limitation to the claim requiring that the membrane "is to be placed on the outside of each bead." The claim contains no such limitation, Andrx's construction is nonsensical and is in direct contradiction to the ordinary meaning of "said beads being coated," *i.e.*, the beads have already been coated.

C. CLAIM CONSTRUCTION OF THE '866 PATENT

As is the case with the '791 patent, Biovail's constructions of the '866 patent rest squarely on the plain language of the claims and are entirely consistent with the intrinsic record.

Claim 1 of the '866 patent reads, in pertinent part, as follows:

> An orally administrable controlled-release composition comprising a pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof . . . said orally administrable composition:
> A) in vitro exhibits the following in vitro release characteristics;
> (i) releases the diltiazem or a pharmaceutically acceptable salt thereof into an aqueous medium at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
> (a) between about 1% and about 15% after about 2 hours;
> (b) between about 7% and about 35% after about 4 hours;
> (c) between about 30% and about 58% after about 8 hours;
> (d) between about 55% and about 80% after about 14 hours;
> (e) in excess of about 75% after about 24 hours; and/or

> (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:
> (a) between about 1% and about 25% after about 2 hours;(b) between about 7% and about 45% after about 4 hours;(c) between about 30% and about 68% after about 8 hours;(d) in excess of about 75% after about 24 hours; and further wherein said orally administrable composition having said in vitro release characteristics results in a composition that:
> B) when orally given to humans exhibit the following properties:
> (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
> (ii) bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria; and
> (iii) provides a Cmax of diltiazem in the blood at between about 10 hours and 15 hours after administration. [12 A-137 (23:19-24:22).]

Andrx's constructions, on the other hand, improperly read language from the patent specification and extrinsic evidence directly into the claims, contrary to the principles of claim construction. Further, Andrx impermissibly asks the Court to subsume the Court's claim construction analysis with factual determinations as to the meaning and interpretation of extrinsic evidence. *See Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1148, 1455-1456 (Fed. Cir. 1988) (reaffirming the Supreme Court's unanimous decision in *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) that "claim construction is a pure issue of law" and does not involve subsidiary or underlying questions of fact.).

1. "method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water"

'866 Claim Terms	Biovail's Construction	Andrx's Construction
"method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water"	Plain meaning -- dissolution testing is conducted according to the methodology set forth in USP 23 at 100 rpm in 900 ml of water.	The dissolution testing is conducted according to USP 23, p. 1791 using Apparatus 1 (basket), 100 rpm, 900 ml of water as defined in the USP, employing the recited acceptance table, i.e the mean average % released of a minimum of six vessels with the detection of drug release being measured by UV absorption at the wavelength of 240 nm.

Biovail's construction of this claim language relies on the plain language of the claim. Claim 1 states that *in vitro* release (or dissolution) is measured according to the methodology of the United States Pharmacopeia ("USP") 23 at 100 rpm in 900 ml of water. [12 A-137 (23:49-51).] The claim does not limit the type of apparatus to be used -- nor does the USP.

Andrx's construction is a classic example of improperly reading language from the patent specification into the claims and, significantly, only the specification language it has determined will be helpful to its case. Specifically, Andrx adds a limitation to the use of a specific dissolution apparatus -- "Apparatus 1 (basket)." Andrx's stated support for this limitation is not the plain and ordinary meaning of the claims, but instead the '866 patent specification at column 12, line 46 to column 13, line 18. [D.I. 142, Exh. B, p. 6.] *See Phillips* at 1312. ("'The written description part of the specification itself does not delimit the right to exclude. That is the function and purpose of the claims.'" quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995)). Notably, a review of the '866 patent specification makes plain that the inventors appreciated when to and when not to specify the use of a particular apparatus.

For example, the language of the patent specification at Column 5, lines 28-61 is identical to the claims and is not limited to the use of any particular apparatus. [12 A-128 (5:28-61); *see e.g.*, 12 A-127 (3:44-45, 62).]

Andrx also adds limitations of "employing the recited acceptance table" and use of a specific UV absorption wavelength for dissolution testing. None of these limitations are actually contained in the '866 patent claims. The words of Claim 1 are unambiguous: *in vitro* release is measured according to the methodology of the United States Pharmacopeia ("USP") 23 at 100 rpm in 900 ml of water. Andrx's proposed construction is based on hand-picking sections of USP 23. [D.I. 142, Exh. B, p. 6.] As can be seen from even a cursory review of Tab 20 of the Joint Appendix, USP 23 is technical reference of many pages, sections, and sub-sections used by those skilled in the art. In essence, Andrx is asking this Court in the context of the Court's claim construction analysis to make factual determinations as to the meaning and interpretation of USP 23. This is improper. *See Cybor Corp.*, 138 F.3d at 1455-1456 (Fed. Cir. 1988) ("claim construction is a pure issue of law" and does not involve subsidiary or underlying questions of fact.) The disputed term should be given its plain and ordinary meaning.

2. "method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium"

'866 Claim Terms	Biovail's Construction	Andrx's Construction
"method of United States Pharmacop0eia No. XXIII at 100 rpm in 900 ml of the buffered medium"	Plain meaning -- dissolution testing is conducted according to the methodology set forth in USP 23 at 100 rpm in 900 ml of the buffered medium.	The dissolution testing is conducted according to USP 23, p. 1791 using Apparatus 1 (basket), 100 rpm, 900 ml of an aqueous medium having a pH between 5.5 and 6.5 and a USP buffer such as 0.05 M phosphate buffer that is prepared according to USP methodology and further, employing the recited acceptance table, i.e., the mean average % released of a minimum of six vessels with the

		detection of drug release being measured by UV absorption at the wavelength of 240 nm.

Biovail's construction of this claim language relies on the plain language of the claim. Claim 1 states that *in vitro* release (or dissolution) is measured according to the methodology of the United States Pharmacopeia ("USP") 23 at 100 rpm in 900 ml of buffered medium having a pH between about 5.5 and about 6.5. [12 A-137 (23:62-24:10).]

Andrx's construction is in the same vain as its construction of disputed term 1 of the '866 patent above. It adds a limitation to the use of a specific dissolution apparatus, "employing the recited acceptance table" and the use of a specific UV absorption wavelength for dissolution testing. As stated above, Andrx not only reads language from the patent specification into the claims, it improperly asks this Court to make factual determinations as to the meaning and interpretation of USP 23. The disputed term should be given its plain and ordinary meaning.

3. "higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria"

'866 Claim Terms	Biovail's Construction	Andrx's Construction
"higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria"	means the composition gives a night vs. day dosing ratio of >1 for AUC and Cmax when given without food.	"higher bioavailability" refers to a formulation when administered at night under appropriate test parameters that exhibits an AUC and a Cmax that exceed the 90% confidence interval as determined according to FDA guidelines of the AUC and Cmax of the same formulation administered in the morning under appropriate test parameters. The appropriate test parameters are defined in "GUIDANCE ORAL EXTENDED (CONTROLLED) RELEASE DOSAGE FORMS IN VIVO

		BIOEQUIVALENCE AND IN VITRO DISSOLUTION TESTING" prepared under 21 CFR 10.90(b)(9) by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence Office of Generic Drugs dated Sep. 3, 1993 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs, Center for Drug Development Research dated Sep. 4, 1993. The data from the study should be analyzed as defined in "GUIDANCE STATISTICAL PROCEDURES FOR BIOEQUIVALENCE STUDIES USING A STANDARD TWO-TREATMENT CROSSOVER DESIGN" prepared under 21 CFR 10.90(b) by Mei-Ling Chem, Ph.D., Division of Bioequivalence Review Branch II dated June 12, 1992 and Rabindra Patnaik, Ph.D., Division of Bioequivalence Review Branch II dated June 26, 1992, approved by Shirkant V. Dighe, Ph.D., Director, Division of Bioequivalence dated June 29, 1992 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs dated June 29, 1992.

Biovail's construction is consistent with the plain language of the claims. The FDA guidelines referred to in the disputed term are the FDA guidance documents disclosed at Column 8, line 14 - Column 12, line 12. [12 A-129-131.] As explained in the patent specification, the key FDA pharmacokinetic parameters for "bioavailability" and "bioequivalence" studies are AUC (the area under the curve in a plot of concentration of drug in the blood against time) and Cmax (the peak plasma concentration of the drug). [*See e.g.*, 12 A-130 (10:36-45).] Thus, this claim term specifies that the composition must provide a higher bioavailability (AUC and Cmax) when the composition is given at night compared to when given in the morning without food according to the FDA guidelines or criteria. The language "higher" should be understood in its plain and

ordinary meaning, *i.e.*, greater than 1. Indeed, the patent specification is consistent with this interpretation:

> . . . according to another aspect of the invention, the results of biostudies employing a formulation according to an embodiment of the invention, clearly show that when given at different times (P.M. or A.M. dosing) under different conditions (with and without food) though they achieve their maximum bioavailability at the same Tmax, when the formulations is given at night (no food) a higher bioavailability (for example ***a significantly higher bioavailability exceeding 25% (Cmax)*** is attained than when given in the morning without food (according to FDA guidelines). [12 A-131 (12:13-22) (emphasis added).]

The file history of the '866 further makes this term plain. For example, in distinguishing two products, Cardizem® CD and Tiazac®, from the'866 invention, the inventors pointed out that night administration of Cardizem® CD and Tiazac® did not result in higher bioavailability as compared to day time administration. [16 A-481-95 (February 4, 2004 Amendment).] To make this point, the inventors presented data to the patent examiner demonstrating that the night/day ratios for the invention was greater than 1 whereas the same ratios for Cardizem® CD and Tiazac® were less than one. [17 A-657-667 (Mathiowitz Declaration, Exhibits 6 and 7).]

Andrx, on the other hand, argues that "higher bioavailability" refers to a formulation that, when administered at night under test parameters purportedly defined in the FDA guidelines, exhibits an AUC and a Cmax that exceed the 90% confidence interval of the AUC and Cmax of the same formulation administered in the morning under appropriate test parameters. Andrx's construction strays from the claim language and improperly asks the Court to make factual determinations as to the meaning and interpretation of the FDA guidelines. For example, Andrx seeks to rewrite the language

"higher" to mean "exceed the 90% confidence interval" based on its interpretation of the FDA guidance documents disclosed in the patent specification. It is also apparent that Andrx is trying to impress upon this Court its interpretation that the FDA guidance documents identify "appropriate test parameters." Moreover, Andrx's construction suggests that the disputed term means the formulation is bioinequivalent when administered in the recited manner. Such a construction is improper as it would read out the embodiment of the invention disclosed in Figures 9A and 9B. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996) (a claim interpretation that excludes a preferred embodiment "is rarely, if ever, correct and would require highly persuasive evidentiary support, which is wholly absent in this case.").

4. "bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria"

'866 Claim Terms	Biovail's Construction	Andrx's Construction
"bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria"	Plain meaning -- food does not render the composition bioinequivalent when the composition is given in the morning with or without food.	"bioequivalence" refers to a formulation when given in the morning with or without food under appropriate test parameters that exhibits an AUC and a Cmax within the 90% confidence interval as determined according to FDA guidelines of the AUC and Cmax of the same formulation administered in the morning under appropriate test parameters. The appropriate test parameters are defined in "GUIDANCE ORAL EXTENDED (CONTROLLED) RELEASE DOSAGE FORMS IN VIVO BIOEQUIVALENCE AND IN VITRO DISSOLUTION TESTING" prepared under 21 CFR 10.90(b)(9) by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence Office of Generic Drugs dated Sep. 3, 1993 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs, Center for Drug Development Research dated Sep. 4, 1993. The data

		from the study should be analyzed as defined in "GUIDANCE STATISTICAL PROCEDURES FOR BIOEQUIVALENCE STUDIES USING A STANDARD TWO-TREATMENT CROSSOVER DESIGN" prepared under 21 CFR 10.90(b) by Mei-Ling Chem, Ph.D., Division of Bioequivalence Review Branch II dated June 12, 1992 and Rabindra Patnaik, Ph.D., Division of Bioequivalence Review Branch II dated June 26, 1992, approved by Shirkant V. Dighe, Ph.D., Director, Division of Bioequivalence dated June 29, 1992 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs dated June 29, 1992.

Biovail's construction again is based on the plain meaning of the claim language. The plain words of the claim state that when the composition is given in the morning with food or without food the formulation is bioequivalent, *i.e.*, meets the FDA guidelines or criteria for bioequivalence. As stated above, the key FDA pharmacokinetic parameters for "bioequivalence" studies are AUC and Cmax. [*See e.g.*, 12 A-130 (10:36-45).]

Andrx's construction of this term, like its proposed construction of term 3 of the '866 patent, strays from the claim language and improperly asks the Court to make factual determinations as to the meaning and interpretation of the FDA guidelines. For example, Andrx seeks here again to impress upon the Court its misleading interpretation that the FDA guidance documents identify "appropriate test parameters."

CONCLUSION

For the foregoing reasons, Biovail respectfully requests that the Court adopt its constructions of the disputed claim terms of the '791 and '866 patents.

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on March 30, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

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